I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on 20 MAY 2009.

Jeff Lloyd, Patent Attorney, Reg. No. 35,589

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. USF.167XC1
Patent No. 7,323,333

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Pablo Caviedes, Raúl Caviedes, Thomas B. Freeman, Juan A. Asenjo, Barbara A. Andrews, Dario Sepúlveda, Christian Arriagada, Julio Salazar Rivera
Issued	:	January 29, 2008
Patent No.	:	7,323,333
For	:	Materials and Methods for Regulating Process Formation in Cell Culture

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 5, line 7:	Page 7, line 13:
"(Ca^2+)"	--(Ca^{2+})--

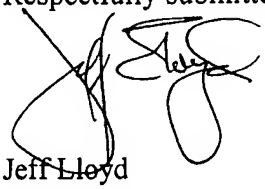
Column 14, line 6:	Amendment dated June 5, 2007 (original claim 18, renumbered as claim 1):
"uM"	--μM--
Column 14, line 19:	Amendment dated June 5, 2007 (original claim 26, renumbered as claim 6):
"uM"	--μM--
Column 14, line 29:	Amendment dated June 5, 2007 (original claim 34, renumbered as claim 10):
"um to 200 um"	--μM to 200 μM--
Column 14, line 59:	Amendment dated June 5, 2007 (original claim 39, renumbered as claim 20):
"uM"	--μM--
Patent Reads:	**Examiner's Amendment accompanying Notice of Allowance dated September 14, 2007 should read:**
Column 15, line 15:	Original claim 40, renumbered as claim 26:
"uM"	--μM--
Column 16, line 2:	Original claim 41, renumbered as claim 29:
"uM"	--μM--
Column 16, line 25:	Original claim 60, renumbered as claim 36:
"The cell culture of"	--The method of--

A true and correct copy of page 7 of the specification as filed, a copy of the Amendment Under 37 CFR 1.111 dated June 5, 2007, and a copy of the Examiner's Amendment accompanying the Notice of Allowance dated September 14, 2007 which support Applicants' assertion of the errors on the part of the Patent Office accompany this Certificate of Correction.

Applicants note that the preamble of original dependent claim 60 (renumbered as claim 36) in the Examiner's Amendment accompanying the Notice of Allowance should read "The method" since it depends from original independent claim 43 (renumbered as claim 35).

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



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JL/dc/abt
Attachments: Copy of page 7 of the specification
Copy of Amendment Under 37 CFR 1.111 dated June 5, 2007
Copy of Examiner's Amendment accompanying Notice of Allowance dated September 14, 2007
Certificate of Correction

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,323,333

APPLICATION NO.: 10/815,388

DATED : January 29, 2008

INVENTORS : Pablo Caviedes, Raúl Caviedes, Thomas B. Freeman, Juan A. Asenjo, Barbara A. Andrews, Dario Sepúlveda, Christian Arriagada, Julio Salazar Rivera

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5,
Line 7, "(Ca^2+)" should read --(Ca^{2+})--.

Column 14,
Line 6, "uM" should read --μM--.
Line 19, "uM" should read --μM--.
Line 29, "um to 200 um" should read --μM to 200 μM--.
Line 59, "uM" should read --μM--.

Column 15,
Line 15, "uM" should read --μM--.

Column 16,
Line 2, "uM" should read --μM--.
Line 25, "The cell culture of" should read --The method of--.

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process-forming cells can be cultured in low calcium (Ca^{2+}) or calcium-free media. In another embodiment, the method of the subject invention involves culturing one or more process-forming cells on a solid substrate that lacks cell attachment factors or that has not been treated to promote cell attachment, as described above, wherein the cells are also cultured under low calcium or calcium-free conditions.

In each of the embodiments disclosed herein, the culture conditions are such that aggregation or clustering of individual cells is promoted and adhesion of the cells to the substrate is inhibited. Preferably, the process-forming cells attain a three-dimensional structure (forming a cluster of cells), grow process-free, with no attachment or minimal attachment to any supporting substrate, and are capable of reproducing cell-cell interactions *in vitro* which normally occur *in vivo*. Therefore, the cells can be manipulated *in vitro* and subsequently harvested without trauma to the cells.

As used herein, the terms "low calcium (Ca^{2+}), or "low calcium (Ca^{2+}) conditions", or grammatical variations thereof, with regard to the cell culture, are intended to mean a total calcium concentration of up to about 100 μM within the cell culture. Preferably, the calcium concentration of the cell culture is 50 μM or less. It is preferred that the culture medium utilized contains no calcium as a component, *i.e.*, the media lacks Ca^{2+} in its formulation; however, it is possible that contaminating levels of calcium (up to about 40 μM - 50 μM) are present within water used to prepare the media. This situation also represents a "low calcium (Ca^{2+}) condition" according to the methods of the subject invention.

A variety of culture media can be utilized to culture process-forming cells according to the methods of the subject invention. For example, if low calcium conditions are desired, Minimum Essential Medium (MEM), Joklik modification for suspension culture, with L-Glutamine, without calcium chloride and sodium bicarbonate (SIGMA, St. Louis, MO; Product No. M0518), or other low calcium media can be used (Eagle, H. *et al.*, *J. Biol. Chem.*, 214:845-847, 1956; Eagle, H., Media for Animal Cell Culture, Tissue Culture Association Manual, 3:517-520, 1976; Eagle, H., *Science*, 130:432-437, 1959; Eagle, H., *Science*, 122:501, 1955).

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on June 5, 2007.

Glenn P. Ladwig, Patent Attorney

AMENDMENT UNDER 37 C.F.R. §1.111
Examining Group 1651
Patent Application
Docket No. USF-167XC1
Serial No. 10/815,388

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Allison M. Ford
Art Unit	:	1651
Applicants	:	Pablo Caviedes, Raul Caviedes, Thomas B. Freeman, Juan A. Asenjo, Barbara A. Andrews, Dario Sepúlveda, Christian Arriagada, Julio Salazar Rivera
Serial No.	:	10/815,388
Filed	:	March 31, 2004
Confirm. No.	:	7583
For	:	Materials and Methods for Regulating Process Formation in Cell Culture

MS AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. §1.111

Applicants request that the period for response be extended two months through and including June 5, 2007, the fees for which have been paid at the time this Amendment was filed.

In response to the Office Action dated January 5, 2007, please amend the above-identified application as follows:

In the Claims

Claims 1-17 (Cancelled)

Claim 18 (Previously presented): A cell culture comprising process-forming neuronal cells of the central nervous system; culture medium; and a solid substrate supporting said culture medium. wherein said neuronal cells lack processes and are clustered into one or more aggregates suspended in said culture medium, wherein there is no attachment of said neuronal cells to said substrate, and wherein said culture has a calcium concentration of 100 μM or less.

Claims 19-20 (Cancelled)

Claim 21 (Previously presented): The cell culture of claim 18, wherein said solid substrate comprises polystyrene and has an untreated surface for supporting said culture medium.

Claim 22 (Previously presented): The cell culture of claim 21, wherein said solid substrate is a culture vessel selected from the group consisting of a Petri dish, flask, bottle, plate, tube, and vial.

Claim 23 (Previously presented): The cell culture of claim 18, wherein said solid substrate comprises untreated plastic.

Claim 24 (Previously presented): The cell culture of claim 21, wherein said solid substrate is a microbiological plate.

Claim 25 (Previously presented): The cell culture of claim 18, wherein said solid substrate has a surface supporting said culture medium, and wherein said surface lacks charged molecules.

Claim 26 (Previously presented): The cell culture of claim 18, wherein said cell culture has a calcium concentration of 50 μM or less.

Claims 27-29 (Cancelled)

Claim 30 (Previously presented): The cell culture of claim 18, further comprising process-forming cells other than said neuronal cells.

Claim 31 (Previously presented): The cell culture of claim 18, further comprising non-process-forming cells.

Claim 32 (Cancelled)

Claim 33 (Previously presented): The cell culture of claim 18, wherein said culture medium lacks calcium ion as a formulated component.

Claim 34 (Previously presented): The cell culture of claim 18, wherein each of said one or more aggregates has an average diameter in the range of 150 μm to 200 μm.

Claim 35 (Previously presented): The cell culture of claim 18, wherein said neuronal cells within each of said one or more aggregates include living cells that remain viable *in vivo* upon implantation.

Claim 36 (Previously presented): The cell culture of claim 18, wherein said neuronal cells are fully differentiated.

Claim 37 (Previously presented): The cell culture of claim 18, wherein said neuronal cells are brain cells.

Claim 38 (Previously presented): The cell culture of claim 18, wherein said neuronal cells are human cells.

Claim 39 (Previously presented): A cell culture comprising process-forming neuronal cells of the central nervous system; and an untreated, polystyrene microbiological plate, wherein said neuronal cells lack processes, are supported by said plate, and are clustered into one or more aggregates, wherein there is no attachment of said neuronal cells to said plate, and wherein said culture has a calcium concentration of 100 μM or less.

Claim 40 (Withdrawn): A method for producing the cell culture of claim 18, comprising placing the neuronal cells on the solid substrate or culture medium; and culturing the neuronal cells for a period of time sufficient for said neuronal cells to cluster into said one or more aggregates.

Claim 41 (Withdrawn): A method for producing the cell culture of claim 39, comprising placing the neuronal cells on the plate; and culturing the neuronal cells for a period of time sufficient for said neuronal cells to cluster into said one or more aggregates.

Claim 42 (Withdrawn): A method for preparing process-forming neuronal cells for transplantation, comprising providing said cell culture of claim 18; removing said one or more aggregates from said culture; and combining said one or more aggregates with a pharmaceutically acceptable carrier.

Claim 43 (Withdrawn): A method for preparing process-forming neuronal cells for transplantation, comprising providing said cell culture of claim 39; removing said one or more aggregates from said culture; and combining said one or more aggregates with a pharmaceutically acceptable carrier.

Claim 44 (Previously presented): The cell culture of claim 18, wherein said neuronal cells are primary cells.

Claim 45 (Previously presented): The cell culture of claim 18, wherein said neuronal cells are cells of a cell line.

Claim 46 (Previously presented): The cell culture of claim 39, wherein said neuronal cells are primary cells.

Claim 47 (Previously presented): The cell culture of claim 39, wherein said neuronal cells are cells of a cell line.

Claim 48 (New): The cell culture of claim 18, wherein said neuronal cells are dopaminergic cells.

Claim 49 (New): The cell culture of claim 39, wherein said neuronal cells are dopaminergic cells.

Remarks

Claims 18, 21-26, 30, 31, and 33-47 were pending in the subject application. By this Amendment, new claims 48 and 49 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Claims 40-43 remain pending but withdrawn from consideration. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. Accordingly, claims 18, 21-26, 30, 31, and 33-49 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants acknowledge that claims 40-43 have been withdrawn from further consideration as being drawn to a non-elected invention. However, the applicants wish to reserve the right to request rejoinder of the non-elected process claims upon an indication of an allowable product claim (cell culture claim) in accordance with MPEP §821.04.

By this Amendment, claims 48 and 49 have been added. Support for claims 48 and 49 can be found, for example, at page 15, line 22; and page 20, lines 2-26 (Example 2), of the specification as filed.

Claims 18, 22-26, and 33 remain rejected under 35 U.S.C. §102(a) as being anticipated by Andrews *et al.* (Poster presentation from Cell Culture and Engineering Conference in Snowmass, CO; 2002). The applicants respectfully traverse. The Declaration under 37 C.F.R. §1.132 by Dr. Caviedes, which was submitted with the applicants' Amendment of January 27, 2006, is sufficient to show that the Andrews *et al.* presentation represents the inventors' own disclosure published less than one year prior to the effective filing date of the subject application.

At page 3, the Office Action acknowledges that the Declaration is sufficient to remove P. Venegas from consideration as "another" for purposes of 35 U.S.C. §102(a). As indicated by Dr. Caviedes in the Declaration, Thomas B. Freeman, Christian Arriagada, and Julio Salazar Rivera also contributed to the claimed invention, but were not included as co-authors of the Andrews *et al.*

presentation because they were not directly responsible for the generation of data contained within the presentation.

The information contained in the Andrews *et al.* presentation represents preliminary work in which the objective was to determine conditions in which cells could be more efficiently cultured in order to obtain large masses of cells in reduced spaces or volumes, with contemplated applications including the extraction of cell products (*e.g.*, neurotrophic factors) and cell transplantation. The contributions of Dr. Freeman, Mr. Arriagada, and Mr. Salazar Rivera were not limited to transplantation methods ("as part of a therapy"); they also contributed to the creation of the cell culture currently claimed.

Dr. Freeman determined the size and geometry of neuronal cell aggregates conducive to cell transplantation (*e.g.*, small clusters of cells to facilitate harvesting and transplant with minimal trauma to the cells), and the culture time and conditions necessary to obtain them. For example, at least some of Dr. Freeman's contributions are embraced by claims 34, 35, and 38. Dr. Freeman was not included as a co-author of the Andrews *et al.* presentation because he participated in the research carried out subsequent to the experiments described in the presentation. Christian Arriagada and Julio Salazar Rivera contributed to the conception of the claimed invention. Mr. Arriagada and Mr. Salazar Rivera designed and carried out morphological experiments to determine when cells in the center of the cell aggregates started to become necrotic (degenerate). In addition, Mr. Salazar Rivera carried out initial transplant studies in Parkinsonian rats. For example, at least some of Mr. Arriagada's and Mr. Salazar Rivera's contributions are embraced by claims 35, 48, and 49. Mr. Arriagada and Mr. Salazar Rivera were not included as co-authors of the Andrews *et al.* presentation because they participated in the research carried out after the experiments described in the Andrews *et al.* presentation.

The subject matter pertaining to the claimed invention that is described within the Andrews *et al.* presentation was invented by Pablo Caviedes, Raul Caviedes, Juan A. Asenjo, Barbara A. Andrews, and Dario Sepulveda. Therefore, the Andrews *et al.* presentation represents the inventors' own disclosure published less than one year prior to the effective filing date of the subject application. As explained above, Thomas B. Freeman, Christian Arriagada, and Julio Salazar Rivera also contributed to the claimed invention, but were not included as co-authors of the Andrews *et al.*

presentation because they were not directly responsible for the generation of data contained within the presentation.

"[O]ne's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar." *In re Facius*, 161 USPQ 294, 301 (CCPA 1969); and MPEP §715.01(c). Therefore, under the authority of *In re Facius*, the disclosure contained in the Andrews *et al.* presentation cannot be used as a prior art reference against the applicants' claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(a) is respectfully requested.

Claims 18, 21-26, 30, 31, 34-39, and 44-47 have been rejected under 35 U.S.C. §103(a) as being obvious over Takazawa *et al.* (U.S. Patent No. 5,219,752) in view of Studer *et al.* (International Published Application No. WO 00/05343) and further in view of Boss *et al.* (U.S. Patent No. 5,411,883). The applicants respectfully traverse.

The cell culture of the invention would not have been obvious to a person of ordinary skill in the art at the time the invention was made, based on the references cited in the Office Action. Submitted with the applicants' Amendment dated October 4, 2006 was a Declaration under 37 C.F.R. §1.132 by Dr. Pablo Caviedes, including Exhibits A-C.

The teachings of the cited references do not provide one of ordinary skill in the art with a reasonable expectation of success in creating a cell culture comprising neuronal cells of the CNS that cluster into aggregates, as recited in independent claims 18 and 39. Only the subject application teaches a cell culture of neuronal cells of the CNS as recited in claim 18. The Takazawa *et al.* patent only provides a reasonable expectation of success in culturing kidney cells as described, not neuronal cells, and certainly not neuronal cells of the central nervous system that cluster into aggregates, as currently recited in the claims.

Claims 18 and 39 of the subject application recite that the cell culture comprises process-forming neuronal cells of the central nervous system and has a calcium concentration of 100 μM or less. The empirical data in columns 17-22 of the Takizawa *et al.* patent indicate that the aggregation of fetal kidney cells essentially occurs when a threshold calcium concentration is reached. In contrast, the inventors of the subject invention have found that process-forming neuronal cells of the central nervous system will aggregate when cultured at a calcium concentration of 100 μM or less.

The Takazawa *et al.* patent proposes that various adherent animal cells can be cultured using the method disclosed therein, including the 500-plus cells tabulated in columns 5-12. These cells represent a very diverse variety of tissues, *e.g.*, bat lung cells, goldfish fin cells, goose sternum cells, human bone marrow cells, human breast cells, human pancreatic cells, mosquito larval cells, moth ovarian cells, snail embryonic cells, viper spleen cells, *etc.* However, the only cells described in the Takazawa *et al.* patent as actually being cultured with the disclosed method are kidney cells, *i.e.*, 293 cells (human fetal kidney) and BHK 229 cells (hamster kidney). In the Declaration submitted on October 4, 2006, Dr. Caviedes indicates:

> absent supporting empirical data, such as that provided in the subject application, one of ordinary skill in the art would not have a reasonable expectation of success in creating a cell culture comprising neuronal cells of the CNS that cluster into aggregates, as recited in claims 18 and 39.

Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The Takazawa *et al.* patent only provides a reasonable expectation of success in culturing kidney cells as described, not neuronal cells, and certainly not neuronal cells of the central nervous system that cluster into aggregates, as recited in the claims of the subject application.

The only cells described as actually being cultured with the disclosed method are kidney cells. A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). As pointed out by the Examiner at page 5 of the Office Action, in a more recent publication, Grinstaff *et al.* report that human fibroblasts and umbilical vein endothelial cells lose their morphology and adhere to untreated polystyrene plates. In view of this "negative teaching", absent supporting empirical data, as provided in the subject application, one of ordinary skill in the art would not have a reasonable expectation of success in creating a cell culture comprising neuronal cells of the CNS that cluster into aggregates, as recited in claims 18 and 39 of the subject application.

At page 4, the Office Action states that "when considering the factors relating to determination of non-enablement, if all the other factors point towards enablement, then the absence or low number of working examples will not by itself render the invention non-enabled." However,

the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness, including a reasonable expectation of success (MPEP section 2142), *i.e.*, reasoning and/or evidence showing why one of ordinary skill in the art would reasonably extrapolate the working example with kidney cells across the entire scope of cells, or at least the process-forming neuronal cells of the CNS currently recited in the claims of the subject application. If the Examiner does not establish a *prima facie* case, the applicants are under no obligation to submit evidence of non-obviousness.

The Examiner's comments at page 5 of the initial Office Action on the merits dated September 27, 2005 seem equally relevant and applicable in considering the references cited by the Examiner here.

> While a single, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the negative teachings of the art and the lack of description and guidance present in the application, provides additional weight to the to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success of creating a cell culture comprising any type of process-forming cells .... (emphasis added)

Furthermore, assuming *arguendo* that the references cited in the Office Action support a reasonable expectation of success in producing the cell culture of the invention, the results obtained using neuronal cells of the cell culture of the invention were significantly better than could have been expected, as shown by Exhibits B and C, which accompanied Dr. Caviedes' Declaration. The experimental results in Exhibits B and C provide a valid comparison for purposes of establishing unexpected results.

As indicated in Example 1, at page 18, lines 27-30, and page 19, lines 1-5, of the subject application, and page 3 of Exhibit B (Materials and Methods—Cell Culture), the RCSN-3 cell line was initially established from a primary culture of the striatum of Fisher 344 rats, and exposed to media conditioned with the UCHT1 cell line (Caviedes R. and Stanbury J.B., *Endocrinology*, 1976, 99:549-554, which is of record). RCSN-3 cells retain the morphology of the neuronal phenotype (Cardenas A.M. *et al.*, *Neuroreport*, 1999, 10(2):363-369, which is of record). Exhibit C shows results from implantation of cells from the same RCSN-3 cell line following culture in the cell culture of the invention. Thus, the RCSN-3 cell line was originally exposed to conditioned media

from the UCHT1 cell line; cells of the cell line were subsequently used in the experiments in Exhibits B and C (and Examples 1 and 2 of the subject application). The cells of Exhibit B were not cultured in the cell culture of the invention. The cells of Exhibit C and Examples 1 and 2 of the application were cultured in the cell culture of the invention.

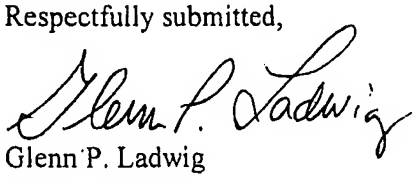
Gradual behavioral recovery (reduction of apomorphine-induced rotation scores) was observed in transplanted animals. As shown in Figure 6 of Exhibit B, rats implanted with conventionally cultured RCSN-3 cells showed a steady decrease in rotations, leveling off at 75% of the initial rotation values after approximately 12-16 weeks post-implant. However, when obtained from the cell culture of the invention described in Example 1 of the subject application, RCSN-3 cells reached a plateau significantly sooner, at approximately 6 weeks post-implant. The comparative data demonstrate that the cell culture of the invention is particularly advantageous for cell transplantation. The benefits of the claimed cell culture are unexpected in view of the prior art, and have a significant, practical advantage. Therefore, the applicants respectfully submit that the cell culture of the invention is not obvious over the cited references. Accordingly, in view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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NOTICE OF ALLOWANCE AND FEE(S) DUE

23557 7590 09/14/2007

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EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/14/2007

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,388	03/31/2004	Pablo Caviedes	USF-167XC1	7583

TITLE OF INVENTION: MATERIALS AND METHODS FOR REGULATING PROCESS FORMATION IN CELL CULTURE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$700	$300	$0	$1000	12/14/2007

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

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If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23557 7590 09/14/2007

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,388	03/31/2004	Pablo Caviedes	USF-167XC1	7583

TITLE OF INVENTION: MATERIALS AND METHODS FOR REGULATING PROCESS FORMATION IN CELL CULTURE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$700	$300	$0	$1000	12/14/2007

EXAMINER	ART UNIT	CLASS-SUBCLASS
FORD, ALLISON M	1651	435-368000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,388	03/31/2004	Pablo Caviedes	USF-167XC1	7583

EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	

23557 7590 09/14/2007.

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

DATE MAILED: 09/14/2007

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No.	Applicant(s)	
	10/815,388	CAVIEDES ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *telephonic interview of 29 August 2007*.

2. ☒ The allowed claim(s) is/are *18,21-23,25,26,30,31 and 33-61*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____.
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Glenn Ladwig on 29 August 2007.

Please use the following version of the claims:

1-17 (Cancelled)

18. A cell culture comprising:

process-forming neurons or glial cells of the central nervous system;

a cell culture medium; and

a solid substrate supporting said cell culture medium;

wherein said neurons or glial cells lack processes, are clustered into one or more aggregates suspended in said cell culture medium, and are not attached to said substrate; and

wherein said cell culture medium has a calcium concentration of 100 uM or less.

19-20. (Cancelled)

21. The cell culture of claim 18, wherein said solid substrate comprises polystyrene and has an untreated surface for supporting said cell culture medium.

22. The cell culture of claim 21, wherein said solid substrate is a culture vessel selected from the group consisting of a Petri dish, flask, bottle, plate, tube, and vial.

23. The cell culture of claim 18, wherein said solid substrate comprises untreated plastic.

24. (cancelled)

25. The cell culture of claim 18, wherein said solid substrate has a surface supporting said cell culture medium, and wherein said surface lacks charged molecules.

26. The cell culture of claim 18, wherein said cell culture medium has a calcium concentration of 50 uM or less.

27-29 (Cancelled)

30. The cell culture of claim 18, further comprising process-forming cells other than said neurons or glial cells of the central nervous system.

31. The cell culture of claim 18, further comprising non-process-forming cells.

32. (Cancelled)

33. The cell culture of claim 18, wherein said cell culture medium lacks calcium ion as a formulated component.

34. The cell culture of claim 18, wherein each of said one or more aggregates has an average diameter in the range of 150 um to 200 um.

35. The cell culture of claim 18, wherein said neurons or glial cells within each of said one or more aggregates includes living cells that remain viable *in vivo* upon implantation.

36. The cell culture of claim 18, wherein said neurons or glial cells are fully differentiated.

37. The cell culture of claim 18, wherein said neurons or glial cells are brain cells.

38. The cell culture of claim 18, wherein said neurons or glial cells are human cells.

39. A cell culture comprising:

process-forming neurons or glial cells of the central nervous system;

a cell culture medium; and

an untreated, polystyrene microbiological plate;

wherein said neurons or glial cells lack processes, are supported by said plate, are clustered into one or more aggregates, and are not attached to said plate; and

wherein said cell culture medium has a calcium concentration of 100 uM or less.

40. A method for producing the cell culture of claim 18, comprising:

placing the neurons or glial cells in the cell culture medium; and

culturing the neurons or glial cells for a period of time sufficient for the neurons or glial cells to cluster into one or more aggregates,

thereby producing a cell culture comprising process-forming neurons or glial cells of the central nervous system, wherein the neurons or glial cells lack cell processes, are clustered into one or more aggregates, and wherein the cell culture medium has a calcium concentration of 100 uM or less.

41. A method for producing the cell culture of claim 39, comprising:

placing the neurons or glial cells in the cell culture medium; and

culturing the neurons or glial cells for a period of time sufficient for the neurons or glial cells to cluster into one or more aggregates,

thereby producing a cell culture comprising process-forming neurons or glial cells of the central nervous system, wherein the neurons or glial cells lack cell processes, are clustered into one or more aggregates, and wherein the cell culture medium has a calcium concentration of 100 uM or less.

42. A method for preparing process-forming neurons or glial cells for transplantation, comprising:

providing said cell culture of claim 18;

removing said one or more aggregates from said culture; and

combining said one or more aggregates with a pharmaceutically acceptable carrier.

43. A method for preparing process-forming neurons or glial cells for transplantation, comprising:

providing said cell culture of claim 39;

removing said one or more aggregates from said culture; and

combining said one or more aggregates with a pharmaceutically acceptable carrier.

44. The cell culture of claim 18, wherein said neurons or glial cells are primary cells.

45. The cell culture of claim18, wherein said neurons or glial cells are cells of a cell line.

46. The cell culture of claim 39, wherein said neurons or glial cells are primary cells.

47. The cell culture of claim 39, wherein said neurons or glial cells are cells of a cell line.

48. The cell culture of claim 18, wherein said neurons are dopaminergic cells.

49. The cell culture of claim 39, wherein said neurons are dopaminergic cells.

50. The cell culture of claim 18, wherein the process-forming neurons or glial cells are neurons.

51. The cell culture of claim 18, wherein the process-forming neurons or glial cells are glial cells.

52. The cell culture of claim 39, wherein the process-forming neurons or glial cells are neurons.

53. The cell culture of claim 39, wherein the process-forming neurons or glial cells are glial cells.

54. The method of claim 40, wherein the process-forming neurons or glial cells are neurons.

55. The method of claim 40, wherein the process-forming neurons or glial cells are glial cells.

56. The method of claim 41, wherein the process-forming neurons or glial cells are neurons.

57. The method of claim 41, wherein the process-forming neurons or glial cells are glial cells.

58. The method of claim 42, wherein the process-forming neurons or glial cells are neurons.

59. The method of claim 42, wherein the process-forming neurons or glial cells are glial cells.

60. The cell culture of claim 43, wherein the process-forming neurons or glial cells are neurons.

61. The method of claim 43, wherein the process-forming neurons or glial cells are glial cells.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
Primary Examiner
Art Unit 1651